SUPPLEMENTAL MATERIAL

Supplementary Table 1. Selected scoring systems for functional status assessment used in patients with AF.

Measure, Year Described	Description	Scores	Design / Validation Cohort	Comments / Limitations
New York Heart Association functional classification for heart failure,[1] 1964	Functional performance measure for categorizing degree of cardiovascular disability	Class I-IV	Designed for symptom grading in cardiac disease Validated in heart failure cohorts, used in multiple AF studies	Advantages: -Easy to use -Useful for its predictive value and as baseline for future evaluations -Used as outcome measure Limitations: -Subjective and insufficiently reproducible
Canadian Cardiovascular Society classification for angina pectoris,[2,3] 1976	Functional classification to stratify severity of angina pectoris	Class I-IV	Designed for symptom grading in ischemic heart disease, used in multiple AF studies	Advantages: -Easy to use -Useful for its predictive value and as baseline for future evaluations Limitations: -Subjective and insufficiently reproducible

Measure, Year Described	Description	Scores	Design / Validation Cohort	Comments / Limitations
Exercise test,[4,5] 1928	Exercise treadmill test with standardized protocol	E.g. Bruce protocol stages 1-9	Designed for diagnosis of angina pectoris, assess functional capacity and hemodynamic response, used in multiple AF studies	Advantages: -Assessment of functional capacity as well as hemodynamic response -Objective -'Gold standard' measure for functional capacity Limitations: -Time-consuming and costly -Uncertain generalizability
Six-minute walk test,[6-8] 1976	Simple test to evaluate distance walked in 6 minutes	Distance in meters	Validated in cardiovascular and pulmonary diseases, including congestive heart failure, and AF	Advantages: -Simple, inexpensive, safe and reproducible -Corresponds more closely to activities of daily living Limitation: -Requires ability to ambulate
Goldman Specific Activity Scale,[9] 1981	Specific Activity Scale for the functional classification with pre-established questionnaire	Class I-IV	Used in multiple AF studies	Advantages: -Higher interobserver reliability and better correlation with exercise time than CCS or NYHA classifications Limitation: -Relatively time-consuming
Duke Activity Status Index,[10]	Self-administered questionnaire with 12 scales (with a different weighting factor) – used to	0-58.2	Validated and correlated to peak oxygen uptake with exercise testing in cardiac	Advantages: -Self-reporting

Measure, Year Described	Description	Scores	Design / Validation Cohort	Comments / Limitations
1989	assess functional activity and quality of life Questions chosen to represent the major aspects of the patient's activity: movement, personal hygiene, housework, sexual activity, and leisure.		patients to measure an individual's maximum potential to perform daily activities	<u>Limitations:</u> -Subjective and no direct measure of exercise performance -May be affected by individual patient emotional and mental factors, as well as cultural or socioeconomic influences

Supplementary Table 2. Selected studies of symptom burden and functional status in AF.

Study, Year Described	Design	Description	N	In- / Exclusion Criteria	Follow-Up	Outcome*
Pharmacological rate- and rhythm control therapies						
PIAF,[11] 2000	Randomized controlled	Rate vs rhythm control	252	Symptomatic persistent AF	12 months	• No difference between rate and rhythm control arms in terms of symptoms • Increased functional capacity with 6 minute walk test • No significant difference in NYHA class
AFFIRM,[12-15] 2002	Randomized controlled	Rate vs rhythm control	4,060	Paroxysmal and persistent AF No severely symptomatic AF	3.5 years	• No difference between rate and rhythm control arms in terms of symptoms • Increased functional capacity with 6 minute walk test • No significant difference in NYHA class • No significant difference in functional capacity with lower heart rates in rate control arm
RACE,[16-18] 2002	Randomized controlled	Rate vs rhythm control	522	Persistent recurrent AF No severely symptomatic AF	2.3±0.6 years	• No difference between rate and rhythm control arms in terms of symptoms • No difference in functional capacity with lower target heart rates in rate control arm
STAF,[19] 2003	Randomized controlled	Rate vs rhythm control	200	Persistent AF	19.6±8.9 months	• No difference between rate and rhythm control arms in terms of symptoms • No significant difference in NYHA class
HOT-CAFÉ,[20] 2004	Randomized controlled	Rate vs rhythm control	205	First episode of persistent AF	1.7±0.4 years	• Increased exercise capacity as measured by exercise treadmill test • No significant difference in NYHA class

Study, Year Described	Design	Description	N	In- / Exclusion Criteria	Follow-Up	Outcome*
Pharmacological rate- and rhythm control therapies						
CTAF,[21,22] 2000	Randomized controlled	Only rhythm control: amiodarone vs sotalol or propafenone	403	Paroxysmal or persistent AF	468±150 days	• Improvement in symptoms in all patients at 3 months
SAFE-T,[23-25] 2005	Randomized controlled	Only rhythm control: amiodarone vs sotalol vs placebo	665	Persistent AF	12-54 months	• Restoration of sinus rhythm resulted in improvement in symptoms and functional capacity • Most significant improvement noted in patients with most severe symptoms at baseline
CONVERT,[26, 27] 2008	Randomized controlled	Only rhythm control: episodic vs continuous amiodarone	209	Persistent recurrent AF	2.1 years	• No difference between episodic and continuous arms in terms of symptoms • Sinus rhythm was associated with an improvement in symptoms in the episodic but not the continuous treated group
RACE II,[28] 2010	Randomized controlled	Lenient vs strict rate control	614	Permanent AF No severely symptomatic AF	3 years	• No difference between lenient and strict rate control arms in terms of symptoms • No significant difference in NYHA class

Study, Year Described	Design	Description	N	In- / Exclusion Criteria	Follow-Up	Outcome*
Non-pharmacological rate control therapies						
Ablate and Pace,[29] 1998	Observational	AVN ablation and PM	156	Medically-refractory symptomatic permanent AF	12 months	• Greater than 30% reduction in symptom checklist scores in patients undergoing AVN ablation and PM
AIRCRAFT,[30] 2003	Randomized controlled	AVN ablation and PM vs pharmacological rate control	99	Medically-refractory symptomatic permanent AF	12 months	• 18% relative reduction in arrhythmia symptom scale in patients undergoing AVN ablation and PM. No change in functional status
AF-SYMPTOMS STUDY,[31] 2004	Crossover	Ventricular response pacing vs no pacing	45	Paroxysmal and persistent AF, standard PM indication (intact AVN)	6 weeks	• Ventricular response pacing reduced symptoms related to AF, however did not affect functional capacity
Non-pharmacological rhythm control therapies						
Weerasooriya et al,[32] 2005	Observational, non-randomized	PVI	63	Paroxysmal AF, failure on 2 AADs	12 months	• Successful PVI improved symptoms, in comparison to failure of PVI
Tondo et al,[33] 2006	Observational, non-randomized	PVI	40 + 65 no LVEF <0.40	Paroxysmal/ persistent AF, LVEF <0.40	14±2 months	• PVI improved functional capacity (6-MWT)
Hsu et al,[34] 2004	Observational, non-randomized	PVI	58 + 58 no CHF	Symptomatic AF, failure on 2 AADs, LVEF <0.45, NYHA >II	12±7 months	• PVI improved both symptoms and functional capacity (NYHA class and exercise test)

Study, Year Described	Design	Description	N	In- / Exclusion Criteria	Follow-Up	Outcome*
Erdogan et al,[35] 2003	Observa-tional	PVI	30	Paroxysmal AF, failure on multiple AADs	34±11 months	• Successful PVI improves symptoms, in comparison to failure of PVI
Oral et al,[36] 2006	Randomized controlled	PVI vs AAD	146	Chronic AF (>6 months)	12 months	• PVI was superior in reducing symptoms • Patients with sinus rhythm had a greater improvement in symptoms than those with recurrent AF
Non-pharmacological rhythm control therapies						
A4,[37] 2008	Randomized controlled	PVI vs AAD	112	Paroxysmal AF, failure on 1 AAD	12 months	• PVI was superior in reducing symptoms and increasing functional capacity
Thermocool AF,[38,39] 2010	Randomized controlled	PVI vs AAD	167	Paroxysmal AF, failure on 1 AAD	9 months	• PVI was superior in reducing symptoms
PABA-CHF,[40] 2008	Randomized controlled	PVI vs AVN ablation + biventricular PM	81	Symptomatic AF, failure on 1 AAD, LVEF <0.40, NYHA >II	6 months	• PVI was superior to AVN ablation and biventricular PM reducing symptom burden

*Includes results of substudies of large randomized trials. 6-MWT = Six-minute walk test; AAD = antiarrhythmic drugs; AVN = atrioventricular node ablation; LVEF = left-ventricular ejection fraction; NYHA = New York Heart Association; PM = Pacemaker; PVI = pulmonary vein isolation
The search strategy included the authors' knowledge of the literature, and computerized searches of PubMed database using the terms "symptoms", "atrial fibrillation", "functional status", "functional capacity", "asymptomatic", "quality of life", "rate", "ablation", "rhythm", "control", alone or in combination. Further selection was based on abstracts and clinical relevance. When available we focused randomized controlled trials, if unavailable we presented important observational studies. Our review is not meant to be conclusive; rather it represents the main studies published on this topic.

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